Nitrenes

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Nitrene Chemistry in Organic Synthesis: Still in Its Infancy?

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alkenes · cascade reactions · heterocycles · homogeneous catalysis · nitrenes

In memory of Walter Lwowski

The element nitrogen is essential to life. Considerable attention is thus paid to the development of synthetic methods for its introduction into molecules. Nitrenes, long regarded as highly reactive but poorly selective species, have recently emerged as useful tools for the formation of C–N bonds. Practical metal-catalyzed protocols are now available for the preparation of amines through either the aziridination of alkenes or the C–H amination of alkanes. Recent results highlighted in this Minireview suggest that synthetic nitrene chemistry is maturing with a wider scope not limited to these two reactions.

1. Introduction

Nitrogen lies at the heart of molecules on which life on earth is based. The structure and function of DNA, proteins, and metal porphyrins perfectly showcase its fundamental role in living systems.[1] It is also widely found in medicines, as illustrated by the recently approved drugs Nesina and Rapiacta for the treatment of type II diabetes mellitus and influenza, respectively.[2] The paramount importance of nitrogen makes the search for new C–N bond-forming reactions a domain still highly investigated today and books published in the last years testify to the recent progress achieved in this area.[3–5] These transformations are often conducted in industrial process chemistry as indicated in a survey of reactions conducted at the Pfizer site in Groton, Connecticut (USA) between 1985 and 2002: C–N bond formation accounts for 15% of the reactions performed.[6] Synthetic methodologies, of course, have benefited from the advent of organometallic catalysis but there is still room for improvement. Suffice to say that nitrogen remains one of the key elements at the center of green chemical research.[7]

Neutral monovalent species with six valence electrons, nitrenes are among the most promising agents for the selective introduction of nitrogen in molecules. Like their carbon cousins, carbenes, their history dates back to the 19th century, more precisely to 1891 when they were proposed by Tiemann as intermediates in the Lossen rearrangement.[8,9] Carbenes and nitrenes display the same reactivity, that is, a high capacity to either rearrange or, more importantly, insert into various bonds, a click-type reaction which started to receive attention in the 1940s and 1950s. Whereas Yates and Doering pioneered the addition of carbenes,[10] Smith described an efficient synthesis of carbazoles based on the cyclization of *o*-azidobiphenyls under thermal or photochemical conditions.[11] These results were followed by other seminal reports from key actors in the field: Smolinsky,[12] Lwowski,[13] Edwards,[14] Breslow,[15] and Anastassiou.[16] These articles document the generation of different classes of nitrenes adding to C–H and C=C bonds to afford C–H aminated products and aziridines, respectively.[8b,17] The yields and selectivities reported for these transformations were generally moderate because free nitrenes are highly reactive and poorly discriminating species. The ability of metal complexes to catalyze nitrene transfers, which was first demonstrated by Kwart and Kahn at the end of the 1960s,[18] opened new avenues for the development of more efficient methodologies that, however, only emerged many years later with the pioneering studies of Breslow,[19] Mansuy,[20] Evans,[21] and Müller.[22] This, and the discovery of practical conditions for the generation of metallanitrenes involving iodine(III) oxidants,[23] make catalytic C–H amination and alkene aziridination now classical tools for the preparation of nitrogen-containing molecules, as highlighted in several recent reviews.[24] Nevertheless, significant work still remains to be done in achieving efficient stereoselective nitrene transfers (Scheme 1).

A closer look at the synthetic application of nitrenes and carbenes, however, reveals a wider scope for carbene chemistry. In addition to catalytic cyclopropanation and

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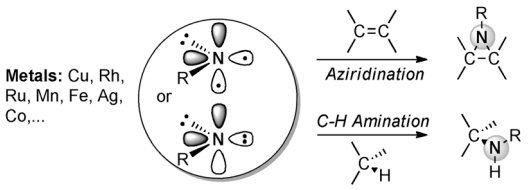
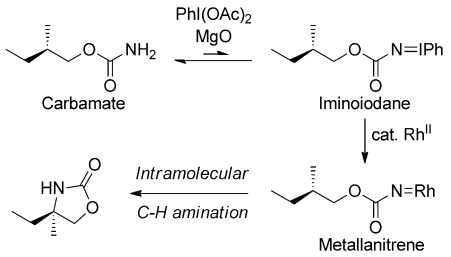


Scheme 1. Classical reactions of nitrenes.

C–H insertion, metal-catalyzed carbene transfer makes it possible to perform X–H insertion (X: O, N, S, Si), the conversion of alkynes to cyclopropenes, and cycloadditions and sigmatropic rearrangements following ylide formation.[25] This led Doyle to point out in 2004 that "*if metal carbene chemistry can be said to be mature, metal nitrene is in its infancy*".[26] It was then suggested that advances comparable to those previously achieved with carbenes could be envisaged in the area of nitrene transfer. This hypothesis is indeed supported by recently published results and this Minireview highlights new alkene difunctionalization reactions, cascade reactions, and heterocycle syntheses based on catalytic nitrene transfers.

2. Catalytic Difunctionalization of Alkenes

Much attention has been paid to the development of methodologies for the catalytic selective difunctionalization of olefins. In these highly useful synthetic transformations two C–X bonds are formed in one reaction, giving access to a variety of key naturally occurring motifs such as 1,2-diols, diamines, and amino alcohols.[27] New conditions for these reactions, which generally rely on the use of osmium or palladium complexes, have recently been described with the aim of addressing the crucial issue of regioselectivity raised by the aminohydroxylation and diamination of nonsymmetrical olefins. Good regiocontrol has been achieved in reactions with "tethered" reaction partners. In parallel, the discovery of procedures involving dirhodium(II)-catalyzed nitrene transfers has provided a relevant alternative for the selective oxidative difunctionalization of olefins. The groups of Rojas[28] and Padwa[29] were the first to recognize the potential of metallanitrenes for the preparation of 1,2-oxyaminated products. Both reported the aminohydroxylation of electron-rich alkenes under conditions analogous to those previously described by Du Bois for intramolecular C–H amination (Scheme 2).[23b] A nitrene is generated by the reaction of a rhodium(II) complex with an iminoiodane, which is



Scheme 2. Pioneering results in intramolecular C–H amination.

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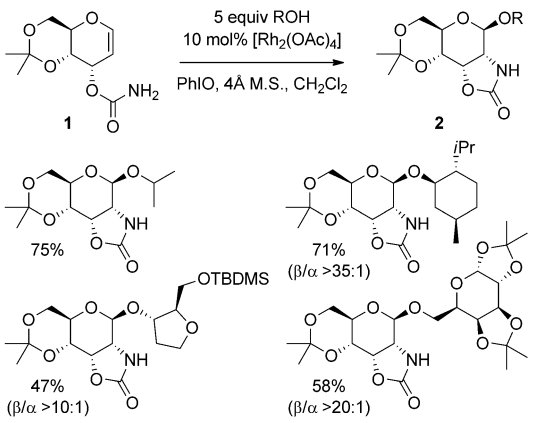
Valerie Pons graduated from the University of Paris Sud XI in 2007. She completed her PhD studies in 2010 under the supervision of Dr. P. Dauban and Dr. R. H. Dodd (Université Paris Sud) on the preparation of indolo-benzazepinones as anticancer agents and the development of indole oxyamidation. After a first postdoctoral position in Prof. W. B. Motherwell's group (University College London), she recently joined the group of Dr. J. C. Cintrat as a postdoctoral associate at Saclay.

Philippe Dauban graduated from ESCIL in 1991. He then completed his PhD research under the supervision of Dr R. H. Dodd (Université Paris Sud, 1996). After postdoctoral studies with Prof. J.-C. Fiaud as a Rhône–Poulenc fellow (ICMO), he took a position at the Institut de Chimie des Substances Naturelles where he is now CNRS Research Director. Research interests of his group include the development of new C–N bond-forming reactions, applications of nitrenes and carbenes in synthetic chemistry, catalytic C–H functionalization reactions, and synthesis of alkaloids and bioactive compounds (anticancer agents and antibiotics).

generated by ligand exchange between a carbamate and the iodine(III) oxidant $PhI(OAc)_2$. The tethered carbamate-derived nitrene and an O nucleophile then add to the C2–C3 double bond of either glycals or indoles to afford the expected 1,2-oxyaminated products.

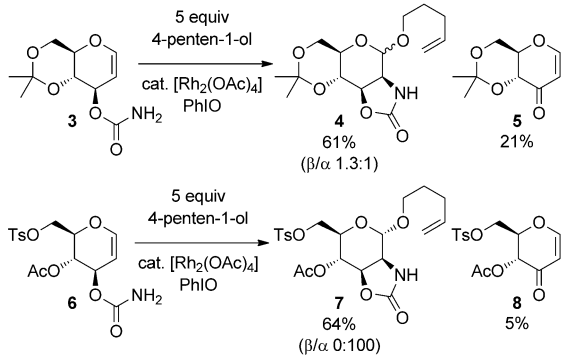
2.1. Difunctionalization of Glycals

Starting from allal 3-carbamates of type **1**,[28] the reaction, which involves sequential C2–N bond formation and β-selective glycosylation, occurs in the presence of various alcohols with excellent regiochemistry and *trans* stereoselectivity, giving access to synthetically useful sugar oxazolidinones **2** (Scheme 3). Use of iodosylbenzene (PhI=O), importantly, prevents the formation of glycosyl acetates arising from addition of the carboxylic acid released by $PhI(OAc)_2$. In addition to rhodium(II) complexes, the amidoglycosylation is catalyzed by copper salts such as $[Cu(MeCN)_4]PF_6$ though with lower efficiency (38–49% yield vs. 47–75% yield in the case of Rh^{II} catalysts). By contrast, application of the same conditions to the analogous glucal 3-carbamate **3**, using 4-



Scheme 3. Amidoglycosylation of allal 3-carbamates. TBDMS = *tert*-butyldimethylsilyl.

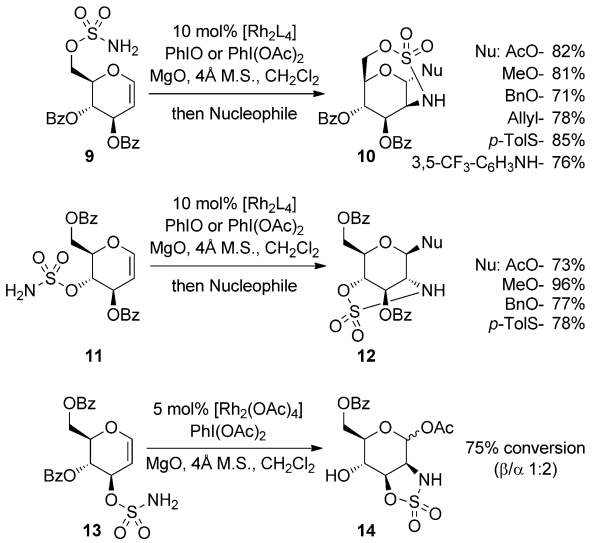
penten-1-ol as the glycosyl acceptor, leads to a 1.3:1 anomeric mixture of readily separable glycosides **4** accompanied by the dihydropyranone by-product **5** (Scheme 4).[30]



Scheme 4. Amidoglycosylation of glucal 3-carbamates. Ts = *para*-toluenesulfonyl.

The formation of **5** is explained by the *ipso* activation of the pseudo-axial electron-rich C3–H bond, mediated by the generated rhodium nitrene.[31] The Rojas group, in addition, has nicely demonstrated the influence of the protecting groups at positions 4 and 6 on the stereo- and chemoselectivity of the reaction.[32] On the one hand, exchanging the isopropylidene group for two benzyl protecting groups favors formation of the α anomer. On the other hand, introduction of electron-withdrawing groups as in compound **6** strongly diminishes the amount of isolated dihydropyranone. Such substitution deactivates the C3–H bond towards oxidation, as a consequence of combined inductive, stereoelectronic, and conformational factors.

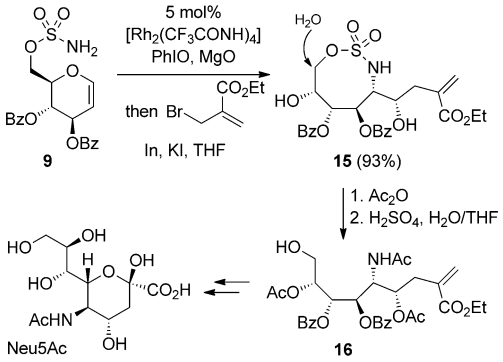
The analogous amidoglycosylation of glycals can also be performed with sulfamates, which are known to be highly efficient nitrene precursors for intramolecular C–H amination or alkene aziridination.[33,34] Liu et al.[35] thus reported the stereoselective preparation of 2-amino-2-deoxy-D-pyranosides by application of rhodium-catalyzed nitrene transfer with various glucals. Substrates like **9**, bearing a sulfamate ester at C6, exclusively afforded 2-amino-α-D-mannopyranosides **10**, whereas compounds like **11** with the sulfamate moiety at C4 gave access to optically pure 2-amino-β-D-glucopyranosides **12** (Scheme 5).[35a] By contrast, a lower level of stereocontrol was observed in the case of glucals having



Scheme 5. Amidoglycosylation of glucal sulfamates. Bz = benzoyl, Bn = benzyl.

a sulfamoyl group at C3. Moreover, as in the case of carbamates, the chemoselectivity of the reaction can be improved by the introduction of electron-withdrawing protecting groups: a C4-sulfamoyl glucal analogous to **11** thus underwent allylic C–H insertion at C3 when this position was substituted by a more electron-rich O-silyl group.[35b]

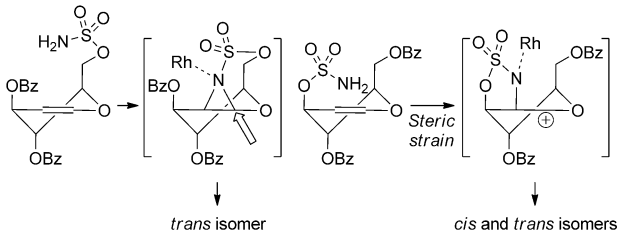
Fundamentally, the use of sulfamates offers many more synthetic opportunities than the use of carbamates. The former allows the introduction of various alcohols, thiols, amines, and allylsilanes as glycosyl acceptors. Moreover, the sulfamate can be displaced by a second nucleophile to give access to unique aminoglycosides. These observations have recently been applied to the synthesis of *N*-acetylneuraminic acid (Neu5Ac), which involves, as the key step, a sequential rhodium-catalyzed nitrene addition and Barbier allylation leading to product **15** (Scheme 6).[36] Finally, in a single relevant example, Du Bois et al. showed that the amidogly-



Scheme 6. Application to the synthesis of Neu5Ac.

cosylation can proceed in an intermolecular manner with comparable levels of regio- and stereoselectivity.[37]

From a mechanistic point of view, DFT calculations carried out by Liu et al. on sulfamate esters[35] support the formation of a rhodium-bound nitrene, whose addition to the glycal double bond is the key step of the reaction. The resulting aziridine–rhodium complex would be highly labile and the regioselectivity of the difunctionalization would be explained by a spontaneous ring opening at the positively charged anomeric carbon (Scheme 7). The *trans* stereoselectivity, on the other hand, would be the consequence of the



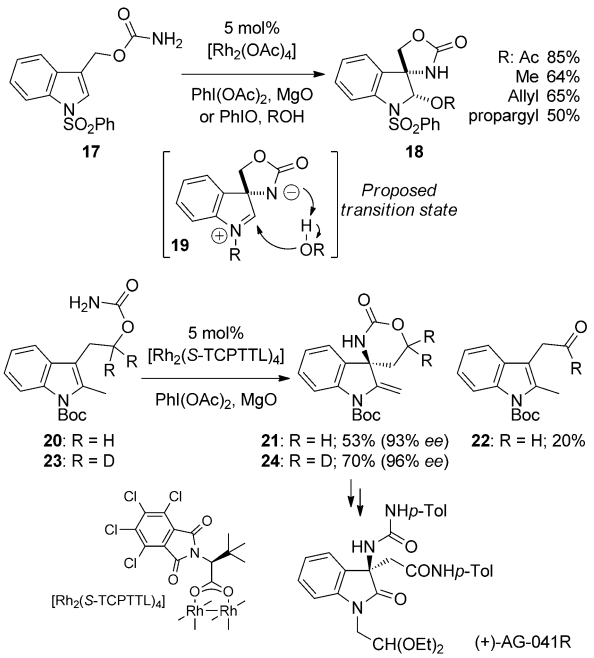
Scheme 7. Mechanistic hypothesis.

S_N2-type nucleophilic ring opening of the aziridine. Such a scenario corroborates the observations made by the Rojas group with allal carbamates. Moreover, the anomeric mixtures obtained starting from glucal carbamates and compound **13** could be the consequence of less stable glycosyl aziridines that would easily afford open oxocarbenium intermediates likely to undergo addition on both faces. However, this mechanism remains hypothetical since aziridine formation has not been demonstrated experimentally so far.

2.2. Difunctionalization of Indoles and Enamides

By tethering a carbamate to the C3 position of indole, Padwa et al. were able to generate a nitrene under the same conditions and observed the analogous oxyamidation of the indole π bond.[29] However, whereas the regioselectivity was comparable to that noted by the Rojas group with glycals, that is, an O nucleophile was introduced at the more electrophilic iminium center, the stereoselectivity observed was totally different: exclusively *cis* products **18** were isolated (Scheme 8). Model experiments with cycloalkenyl carbamates then confirmed that formation of an aziridine followed by its S_N2-type ring opening gives only *trans* isomers. These results suggest the involvement of zwitterionic intermediates of type **19**, possibly resulting from the ring opening of a preformed but very unstable aziridine. Nucleophilic attack would thus take place from the side of the amide anion that would induce the concomitant deprotonation underlying the facial selectivity of the addition.

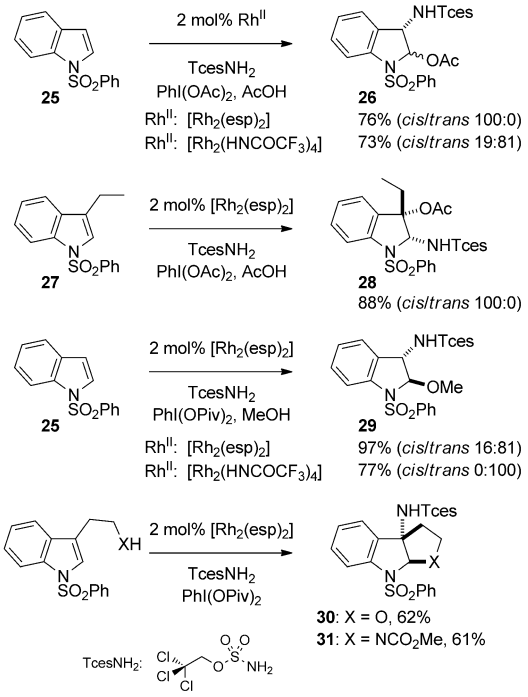
Strikingly, the course of the reaction strongly depends on the substrate. Thus, mixtures of *cis* and *trans* products were isolated from the 2-indolyl and 3-benzofuranyl carbamates.[29] Iwabuchi et al. more recently found that the 2-methylindolyl derivative **20** affords the spirocyclic enamide **21** accompanied



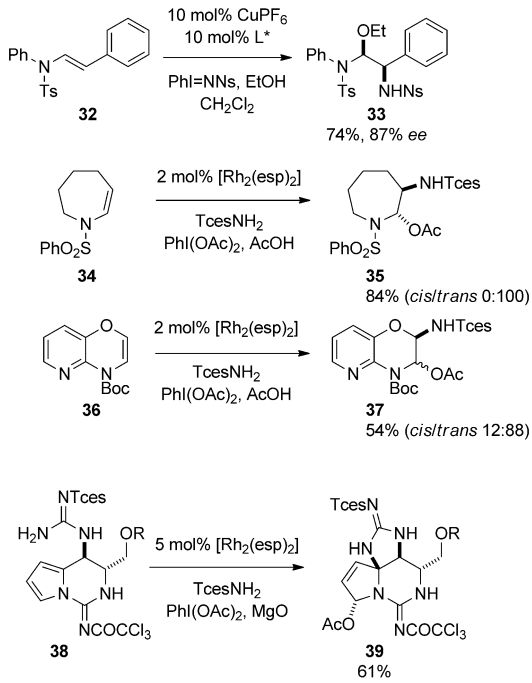
Scheme 8. Intramolecular oxyamidation of indoles. Boc = *tert*-butoxycarbonyl.

by the aldehyde by-product **22**, which arises from hydrogen abstraction α to the carbamate group.[38] Formation of the latter can be suppressed by performing the reaction starting from the deuterated analogue **23**. These results were then applied to the asymmetric synthesis of the potent Gastrin/CCK-B receptor antagonist (+)-AG-041R.

Even more unexpected observations were made in the intermolecular version of indole oxyamidation. By application of conditions initially developed by Du Bois for catalytic intermolecular C–H amination,[39] it has been found that the addition of a trichloroethylsulfamate-derived nitrene can also proceed efficiently to give 1,2-oxyaminated products.[40] Worthy of note are the comparable high levels of regio- and stereocontrol observed for the intermolecular difunctionalization (Scheme 9). The regioselectivity depends on the indole substitution—the sense of the addition is reversed in the case of 3-ethylindole **27**. In contrast, the stereoselectivity varies according to either the O nucleophile or the rhodium complex. Carboxylic acids generally lead to *cis* products in the presence of $[Rh_2(esp)_2]$, whereas use of methanol favors the formation of *trans* isomers. The latter, surprisingly, was obtained almost exclusively when the transformation was catalyzed by the rhodium carboxamidate $[Rh_2(CF_3CONH)_4]$, regardless of the nucleophile introduced. In addition, tethering the nucleophile with the indole gives access to fused tricyclic scaffolds. More importantly, this approach can be used to perform a regioselective 1,2-diamination[40] allowing the introduction of two nitrogen units distinguished by their protecting groups.[41] Initial experiments have also revealed that this chemistry can be applied to the carboamination of alkenes as indicated by the intermolecular reaction with 3,4,5-trimethoxybenzene.[42]



Scheme 9. Intermolecular oxyamidation of indoles. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, Piv = pivaloyl.



Scheme 10. Oxyamidation of enamides and pyrroles.

The scope of the catalytic oxyamidation of alkenes is not confined to indolic derivatives. It has recently been reported that this reaction can also be performed with enamides and enecarbamates.[43] Whereas enantiopure copper salts mediate the asymmetric formation of α-amino aminals from *N*-(styryl)sulfonamides **32** mainly in the presence of ethanol,[43b] dirhodium(II) catalysts prove efficient to induce the production of the expected oxyaminated compounds from diversely substituted cyclic enamides **34**, benzodioxines, and benzoxazines **36** (Scheme 10).[43a] Addition of the O nucleophile, once again, takes place regioselectively at the position α to the nitrogen, preferentially *trans* to the previously inserted TcesNH group. It thus affords N,O-acetals that can be further modified by reaction with several C or N nucleophiles in the presence of a Lewis acid.[43a] Interestingly, other electron-rich heterocycles might be good candidates for the discovery of new reactivities in a broader perspective, as suggested by the result reported by Du Bois with pyrrole **38** during the synthesis of (+)-gonyautoxin 3.[44] The unexpected formation of the 1,4-oxyamidated product **39** clearly shows the synthetic potential of catalytic nitrene transfers.

Drawing a mechanism to rationalize all these observations made with indoles and enamides is challenging. While Padwa et al. in their earlier studies discarded the involvement of an aziridine intermediate, the isolation of *trans* products in intermolecular oxyamidation argues for its formation. However, should such cyclic intermediates be involved in these oxidative processes, these are highly unstable species, probably even more labile than those derived from glycals, which have been neither detected spectroscopically nor trapped experimentally until now. However, the excellent regioselectivity observed makes these reactions useful synthetic tools, for example, for the application of classical iminium chemistry. In parallel, it remains to be seen whether these oxidative transformations can be performed with comparable efficiency from simple alkenes, that is, without heteroatom substituents.

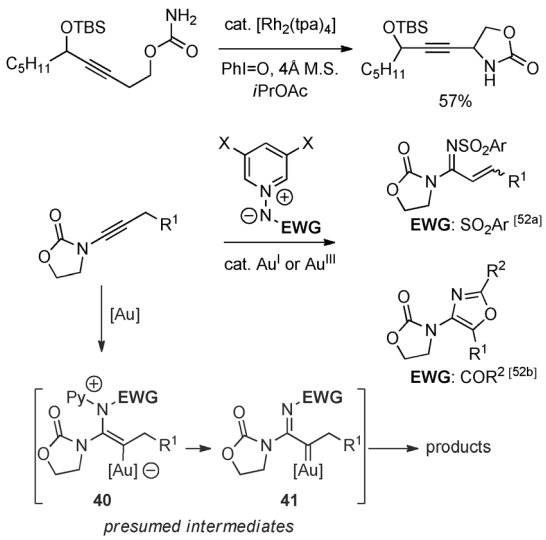
3. Cascade Reactions

The design of new cascade reactions for the preparation of complex molecules is a thoroughly investigated field in synthetic organic chemistry.[45] Sequential one-pot transformations provide rapid access to molecular diversity as well as elegant solutions for the synthesis of natural products. In the context of sustainable chemistry, moreover, cascade reactions offer unique benefits such as atom economy and limited waste production. The use of metallacarbenes, to this end, has been highly productive with the conception of domino reactions for the synthesis of alkaloids that date back to the early 1980s.[46] By comparison, the application of nitrene chemistry to cascade reactions has only recently been considered with the pioneering studies of the group of Blakey.[47]

3.1. Reactions with Alkynes

While cyclopropenation of alkynes is a well-established method for the preparation of cyclopropenes,[48] the addition of nitrenes to alkynyl derivatives has been rarely explored. Earlier attempts to generate the highly unstable antiaromatic 1*H*-azirines by inter- or intramolecular azirination of alkynes failed. These reactions generally led to the isolation of 2*H*-azirines following a presumed rapid rearrangement of puta-

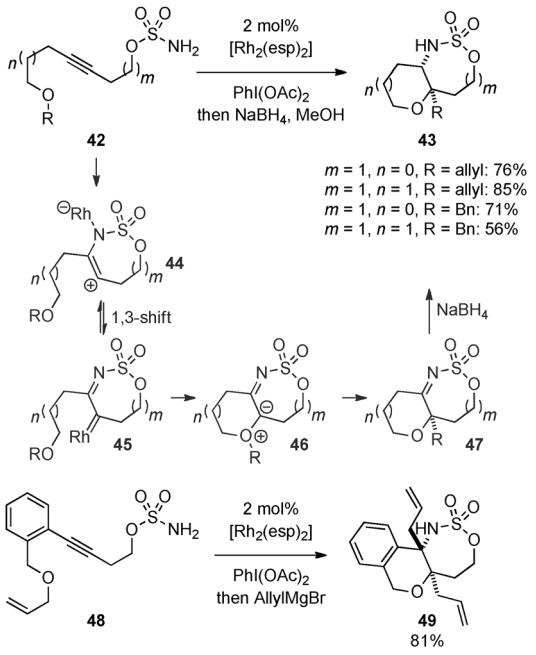
tive 1*H*-azirines,[49] or afforded oxazoles with acylnitrenes.[50] Very recently, the group of Schomaker has reported the first example of intramolecular propargylic C–H amination involving carbamate-derived nitrenes generated by application of Du Bois' conditions (Scheme 11).[51] The resulting oxazo-



Scheme 11. Intramolecular C–H amination of alkynes and gold-catalyzed alkyne transformation. tpa = triphenylacetate, TBS = *tert*-butyldimethylsilyl.

lidinones **41** can then be converted in few steps to densely functionalized tricycles. Other new reactions with alkynes have also been described by combining iminopyridinium ylides with gold catalysts, which leads to the production of either amidines or oxazoles.[52] However, as fairly concluded by the Davies group, these reactions rather involve nitrene equivalents. Addition of the ylides onto gold-activated alkynes followed by elimination of the neutral pyridine ring leads to α-imino gold carbene intermediates that are otherwise difficult to prepare by application of classical gold carbene chemistry.

By comparison, the pioneering studies by Blakey et al., which rely on the rhodium-catalyzed intramolecular delivery of a sulfamate-derived nitrene, represent a significant achievement.[47] Strikingly, no propargylic C–H amination is observed contrary to the case of carbamates, a result that highlights the crucial influence of the nitrene protecting group on its reactivity. Complex polycyclic structures **43** are isolated instead in very good yields of up to 98% from the rather simple substrates **42**, after an extra step of $NaBH_4$-mediated reduction (Scheme 12). The cascade reaction, which includes the sequential formation of a C–N, a C–O, and a C–C bond, would involve the generation of the vinyl cation **44**, which is in equilibrium with the metallacarbene **45** by means of a 1,3 H-shift. Intermediate **45** would be trapped internally by an oxygen lone pair to afford the oxonium ylide **46**, which rearranges to the *N*-(sulfonyl)imine **47**. This could either be isolated or reduced to the more stable amine. Additionally, it has been shown that alkylation of this imine by a Grignard reagent proceeds efficiently as illustrated by compound **49**,

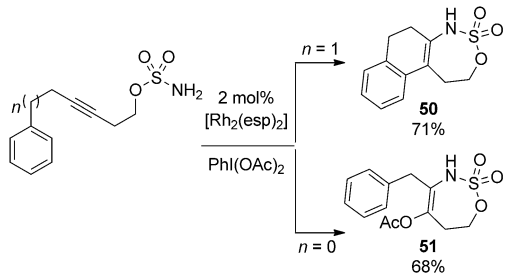


Scheme 12. Cascade reactions starting from alkynyl sulfamates.

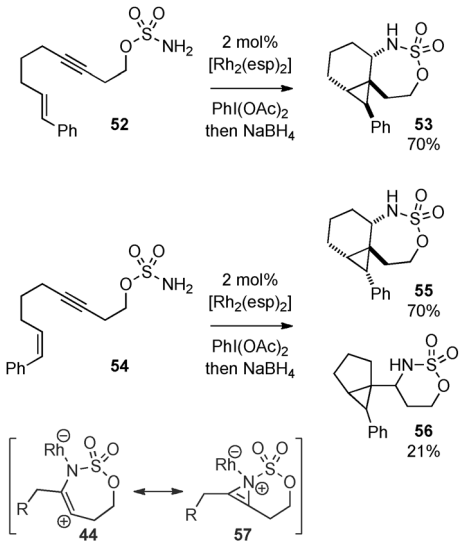
which was obtained in 81% yield. This last step increases the molecular complexity generated in a single vessel.

With the aim of elucidating the exact nature of the intermediates formed during the cascade, Blakey et al. have been able to use other internal traps that allow the production of new polycyclic scaffolds.[53] The involvement of a vinyl cation intermediate has thus been corroborated by the reaction with electron-rich π nucleophiles such as arenes (Scheme 13). Yields have been found to decrease for substrates having aromatic rings with electron-withdrawing substituents. Interestingly, installation of a shorter tether for the benzene ring prevents the expected intramolecular reaction, thereby leading to the product of alkyne oxyamidation **51**. The latter arises from intermolecular nucleophilic attack of the carboxylate unit of the iodine(III) oxidant, a process comparable to that described before with glycals, indoles, and enamides (see Section 2).

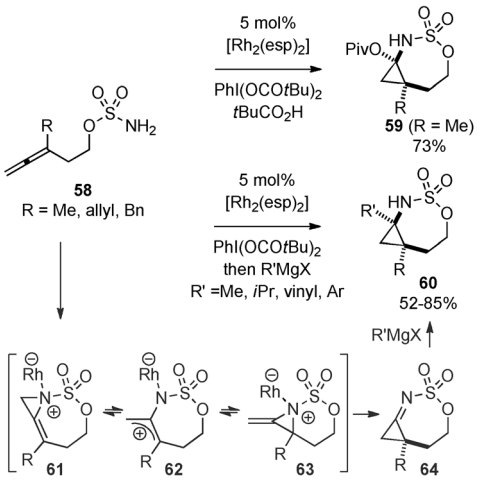
The absence of products resulting from benzylic C–H insertion could have ruled out the involvement of the putative metallacarbene **45**. However, when the aromatic ring was replaced by an alkene the authors could isolate fused cyclopropane derivatives (Scheme 14). Importantly, tethered *trans* and *cis* olefins react stereospecifically to give the



Scheme 13. Cascade reactions with tethered aromatic rings.



Scheme 14. Cascade reactions with tethered alkenes.



Scheme 15. Cascade reactions starting from allenyl sulfamates.

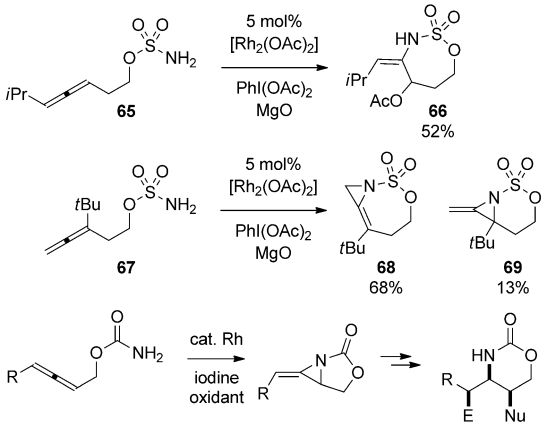
corresponding *trans* and *cis* cyclopropanes, an observation that suggests the concerted insertion of a metallacarbene that would be in equilibrium with the former vinyl cation. Moreover, the formation of regioisomers in the case of the *cis* substrate **54** suggests that this species might exist in the form of a highly strained azirine **57**. Despite the mechanistic issues, these cascade reactions and the subsequent transformations of cyclic sulfamates afford unprecedented molecular architectures that underscore the unique synthetic opportunities provided by nitrenes. Because their reactivity towards alkynes is still not thoroughly explored and well understood, the door remains open to additional investigations.

3.2. Reactions with Allenes

Based on the aforementioned hypotheses, the Blakey group has further envisaged the application of rhodium–nitrene chemistry to allenes in order to produce 2-amidoallyl cations;[54] an analogous study was also carried out in parallel by Robertson et al.[55] Because of the absence of general methods for their preparation, these synthons have received little attention so far, in contrast to their carba and oxa analogues, namely trimethylenemethane and 2-oxyallyl cations. This gap, however, was filled by the use of nitrenes generated from sulfamates. The reaction with *gem*-disubstituted allenes **58** affords strained cyclopropylimines **64** that undergo nucleophilic attack of either pivalic acid or a wide range of Grignard reagents (Scheme 15). The resulting adducts **59** or **60** are isolated with complete stereoselectivity, resulting from introduction of the nucleophile on the convex face of the bicyclic scaffolds. Robertson et al. have demonstrated that the strained N,O-acetals can react further with various nucleophile such as hydrides and malonate anions.[55]

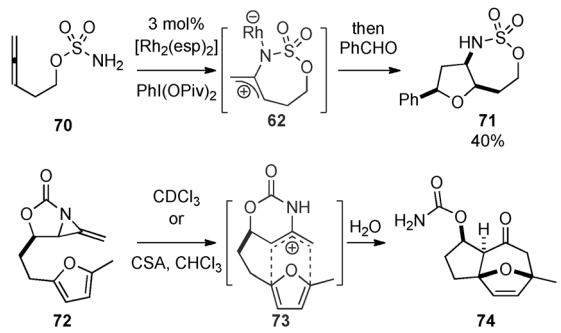
Both research groups have reported that the overall transformation is sensitive to steric effects. The introduction of bulkier *i*Pr or Ph substituents on the allene favors the formation of products such as **66**, resulting from a formal oxyamidation process (Scheme 16).[55] Even more unexpectedly, the presence of a *tert*-butyl group leads to the sole formation of regioisomeric methylene aziridines **68** and **69**. This type of influence of the substitution has also been pointed out by Schomaker et al. in their work related to allene functionalization.[56] Interestingly, their investigations combined with those from the Robertson group[57] have once again revealed a more "classical" behavior for carbamate-derived nitrenes. These mostly led to methylene aziridines with yields of up to 94% but generally accompanied by C–H amination by-products. The subsequent regioselective ring opening of the aziridine makes this methodology appropriate for the functionalization of the three allene carbons.

Understanding the mechanism of this allene functionalization reaction is challenging for organic chemists. Several test experiments have been carried out to this end; they all provide new synthetic opportunities that should be explored in the near future. With the aim of demonstrating the formation of the presumed 2-amidoallyl cation, Blakey et al., for instance, performed the reaction in the presence of a dipolarophile.[54] [3+2] Cycloaddition with benzaldehyde



Scheme 16. Reactions of allenyl sulfamates and carbamates.

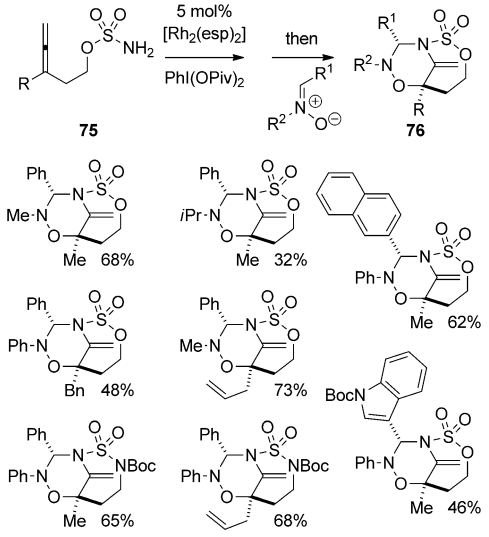
thus allows the isolation of the expected furan **71** with complete regioselectivity and *endo* stereoselectivity, though with a moderate yield of 40% (Scheme 17). Whether the allyl



Scheme 17. Cascade reactions involving [3+2] or [4+3] cycloadditions. CSA = camphorsulfonic acid.

cation **62** arises from the ring opening of a methyleneaziridine, however, remains a matter a debate particularly in the case of sulfamate esters. A first answer, nevertheless, has been provided by experiments carried out by Robertson et al.[57,58] They have been able to generate this type of allyl cationic intermediate by acidic treatment of methyleneaziridine **72**, which in turn was obtained by application of a protocol involving *N*-tosyloxycarbamates.[59] The subsequent intramolecular [4+3] cycloaddition is another type of domino reaction likely to be developed using catalytic addition of nitrenes to allenes.

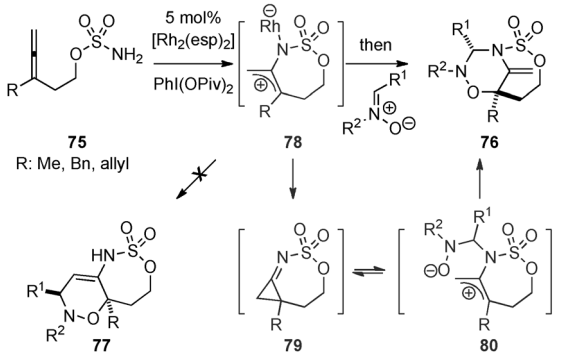
Much more unexpected are the results described by Blakey et al. for allyl cation intermediates subjected to nitrones prepared from aryl- and heteroaryl aldehydes.[60] Whereas nitrones are well-known to undergo [3+2] cycloadditions with a wide range of dipolarophiles, their reaction with homoallenylsulfamate-derived allyl cations led to the formation of [3+3] cycloadducts **76** with yields ranging from 32% to 73% (Scheme 18). The transformation is sensitive to



Scheme 18. Cascade reactions involving [3+3] cycloadditions.

steric effects with respect to the nitrogen group of the nitrone: the *tert*-butyl derivative leads to the fused cyclopropane derivative **59** (R = Me). The sequence also proceeds with equal efficiency with allene *N*-(Boc)sulfamides.

The regiochemistry is clearly unusual: the nitrone adds across the nitrogen and the most substituted carbon terminus of the presumed intermediate **78** to afford compound **76** instead of **77** (Scheme 19). This has been rationalized by the



Scheme 19. Hypothetical mechanism for the [3+3] cycloaddition.

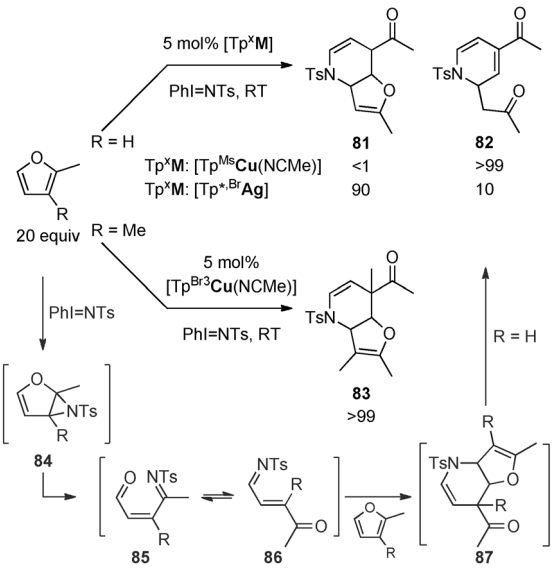
generation of the strained cyclopropylimine **79**, which would subsequently undergo addition with the nitrone. This event would provide an electronic driving force facilitating cyclopropane ring opening, which would generate the allyl cation **80** internally trapped by the oxygen of the nitrone. Such a hypothetical pathway is consistent with the scandium(III) triflate mediated annulation of compound **59** with benzaldehyde which provides a bridgehead product analogous to **76**.

4. Synthesis of Pyridine, Pyrrolidine, and Indole Derivatives

As mentioned earlier in the introduction, the metal-catalyzed aziridination of alkenes is a classical reaction in the nitrene repertoire that can be applied to a wide range of olefins. This efficient transformation, now considered as a standard reaction in heterocycle synthesis, leads to the formation of synthetically useful aziridines. The latter can then undergo either ring opening with C, O, N, or S nucleophiles for the production of 1,2-difunctionalized products,[61] or ring expansion to afford five- and six-membered-ring compounds.[62]

Recent investigations capitalizing on the efficiency of metal-catalyzed alkene aziridination have provided a new access to a variety of heterocycles. Perez et al. have reported an unexpected sequence from furans. The reaction selectively affords 1,2-dihydropyridines which result from the combination of two furan moieties with one NTs unit.[63] Excellent yields of up to 99% are obtained for this unprecedented reaction provided that mono- and disubstituted furans are introduced in excess (Scheme 20).

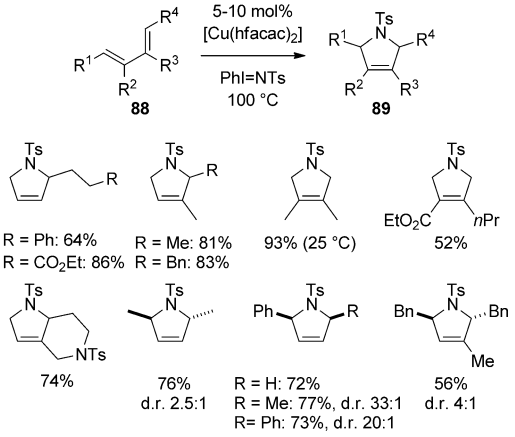
The outcome, however, depends on the nature of the metal as well as on the substitution pattern of the substrates.



Scheme 20. Formation of 1,2-dihydropyridines by the addition of nitrenes to furans. Tp = tris(pyrazolyl)borate.

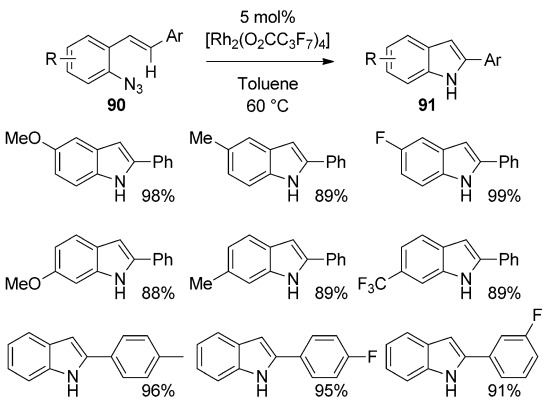
On one hand, while the use of copper-scorpionate complexes induces the formation of 1,2-dihydropyridines **82** from 2-methylfuran, that of the silver analogue preferentially leads to furo[3,2-*b*]pyridine derivatives **81**. This can then be converted to **82** by treatment with neutral alumina. The reaction of 2,3-dimethylfuran affords only the bicyclic compound **83**, which cannot be transformed to the expected dihydropyridine by means of a β-H elimination. Careful NMR investigations have been carried out to elucidate the mechanism of this unusual transformation. The authors come to the conclusion that the reaction would involve an initial furan aziridination affording aziridine **84**. This intermediate, which could not be detected, would undergo an extremely fast rearrangement to give the aldehyde **85**, which readily isomerizes to give the imine **86**. A metal-catalyzed [4+2] cycloaddition with inverse electronic demand would generate the furopyridine scaffold **87**. When R = H, a final step of β-H elimination would proceed to lead to the expected dihydropyridine **82**.

More recently, the copper-catalyzed aziridination of 1,3-dienes has been shown to be of general application for the formation of 3-pyrrolines.[64,65] Very good yields of up to 94% were obtained when the mixture was heated at 100°C in the presence of the commercially available [Cu(hfacac)$_2$] (hfacac=hexafluoroacetylacetonate). Importantly, the fluorine atoms have been found to be key to the success and even higher yields can be obtained with ligands bearing *n*-C_7H_{15} side chains. The reaction can be applied to a large variety of mono-, di-, and trisubstituted 1,3-dienes **88**. Moreover, good diastereoselectivity is observed in the reactions with 1,4-disubstituted substrates (Scheme 21). It has then been shown that the diastereocontrol depends on the substitution pattern rather than on the diene geometry: the presence of an aryl substituent leads to the preferential formation of *cis* compounds while *trans* products are favored when two alkyl groups are introduced. The experimental evidence points to a two-step mechanism: the initial catalytic alkene aziridination is followed by ring expansion efficiently catalyzed by the more Lewis acidic [Cu(hfacac)$_2$] as reported by Njardarson et al.[66,67]

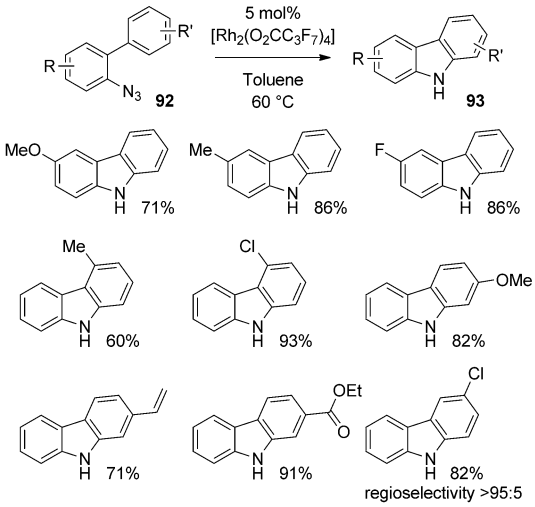


Scheme 21. Formal catalytic [4+1] cycloaddition of nitrenes and 1,3-dienes.

Finally, a new class of reactions has been described with azides though it does not involve a real nitrene intermediate. As mentioned in the introduction, azides have been landmark reagents for the synthesis of nitrogen heterocycles through intramolecular addition.[68] The venerable Hemetsberger–Knittel synthesis of indoles is a good example demonstrating their paramount importance in this domain. Surprisingly, the use of azides as precursors in metal-catalyzed nitrene transfers has long been neglected. They have, however, received renewed interest particularly in combination with dirhodium(II) complexes.[24d,m,q] Driver and co-workers have reported the preparation of indoles and carbazoles that involves the catalytic decomposition of, aryl and biaryl azides **90** and **92**, respectively.[69] The addition to olefins or arenes proceeds with excellent yields of up to 99% in the presence of the highly electrophilic rhodium(II) perfluorobutyrate or rhodium(II) octanoate, and is compatible with either electron-donating or electron-withdrawing substituents (Schemes 22 and 23). Similar transformations have also been described with vinyl azides for the preparation of indoles and pyrro-



Scheme 22. Preparation of indoles from aryl azides **90**.

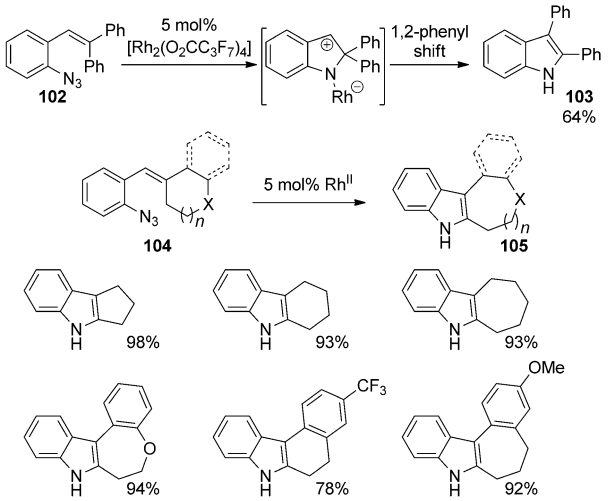


Scheme 23. Preparation of carbazoles from biaryl azides **92**.

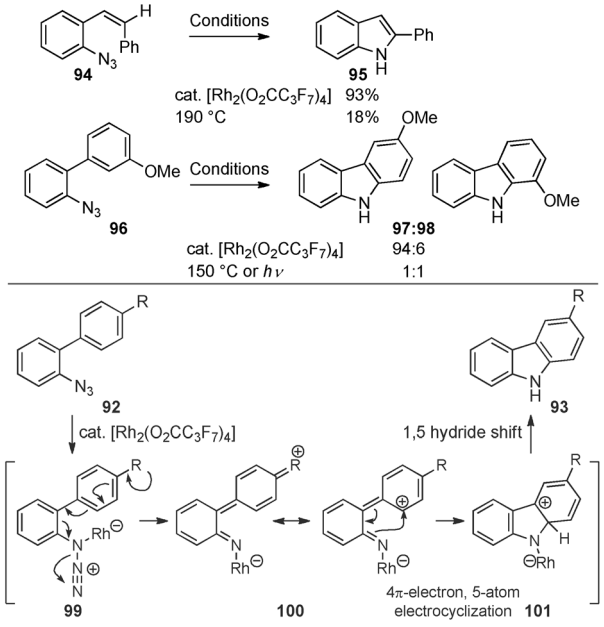
les.[24d,q] In all cases, the nature of the carboxylic ligand installed on the dinuclear core is crucial for the reactivity since no reaction takes place with classical $[Rh_2(OAc)_4]$ or $[Rh_2(5S\text{-mepy})_4]$ (mepy = methyl pyrrolidone-5-carboxylate) while the use of $Rh_2(OCOCF_3)_4$ induces lower conversion.

From a mechanistic point of view, the reaction could be considered a classical insertion of a nitrene into a C–H bond. This simple picture, however, is not consistent with several experimental observations. Previous articles have described the low propensity of dirhodium(II) complexes to decompose azides to nitrenes.[24f,70] Differences in product distribution were also noted depending on whether the rhodium-catalyzed protocol or thermal conditions were applied to *Z*-styryl azide **94** and to biaryl azide **96** (Scheme 24). The Driver group thus performed intramolecular competition experiments that led them to propose the following mechanism.[71] the reaction of the azide with the rhodium catalyst would generate an arylnitrenium ion **100**, which would undergo a 4π-electron, 5-atom electrocyclization to form the new C–N bond. A final 1,5-hydride shift would afford the expected product.

This pathway is corroborated by the reactivity observed in the reaction starting from the *gem*-diphenyl derivative **102**.[69a] Treatment of the latter with rhodium(II) perfluorobutyrate affords the 2,3-disubstituted compound **103** resulting from a 1,2-phenyl shift (Scheme 25). The scope of this reaction has then been extended to a variety of β,β-disubstituted styryl azides **104** for the design of an elegant route to polycyclic indolic scaffolds **105**.[72] Competitive experiments have revealed that more electron-rich aryl groups migrate preferentially, thereby suggesting the involvement of phenonium ion intermediates for the rearrangement.



Scheme 25. Synthesis of polycyclic indoles.



Scheme 24. Mechanism for indole and carbazole formation.

5. Conclusions

This Minireview clearly demonstrates that nitrene chemistry in organic synthesis is no longer limited simply to catalytic C–H amination and alkene aziridination reactions. In the examples described nitrenes are used in the difunctionalization of alkenes with the formation of C–N, C–O, and C–C bonds, in cascade reaction, and in cycloadditions, thereby offering unique access to a variety of unprecedented azacyclic scaffolds. A closer inspection of these recent developments reveals that the field has greatly benefited from the discovery of iodine(III) oxidants as competent reagents for the production of nitrene precursors, as well as from the advent of dirhodium and copper species as highly efficient catalysts to mediate nitrene transfer. Worthy of note is the influence of their associated ligand on the outcome of the transformations. It is therefore expected that new transformations may be described in the near future if one considers the growing number of metal complexes (Ru, Mn, Co, Fe, Ag…) recently reported for C–H amination and alkene aziridination, and the

availability of different nitrene precursors (e.g. azides and haloamines).

The possibility of modifying both substituents on carbene species has led to major breakthroughs in the last few years. Highly chemoselective reactions, for example, have been discovered with the advent of donor–acceptor diazo compounds. By comparison, nitrenes could offer less opportunity with a single substituent likely to be modified. Nevertheless, its influence is clearly evident as shown by the aforementioned switch in reactivity between carbamates and sulfamates. The search for other nitrene sources should therefore pave the way for the invention of new reactions.[73] Taken together, these conclusions thus suggest that the nitrene chemistry is no longer in its infancy. It has slowly matured and reached an age where it should no longer live in the shadow of its carbon cousin.

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